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Research Article

Electronic, Structural and Molecular Implications of Curcumin and its Relationship with Apoptosis in A549 Cells

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Abstract

This research focuses in the computational analysis of the electronic and molecular structure of curcumin, applying density functional theory (DFT) to obtain global reactivity descriptors (GRDs). Furthermore, the energy gap was determined by characterizing the *HOMO-LUMO* frontier molecular orbitals. The resulting electronic fingerprint indicates a highly reactive molecule with a remarkable capacity to donate electrons, giving it an electrophilic character. Curcumin is used in traditional Eastern medicine as an anti-inflammatory, antioxidant, and anticancer agent; it is a natural polyphenol derived from Curcuma longa. Recent research reports that it exhibits significant antitumor activity against non-small cell lung cancer in the A549 cell line model. Our GRDs correlated directly with other experimental studies conducted *in vitro* and *in vivo*, confirming curcumin´s ability to induced programmed cell death through multiple signaling pathways, notably oxidative stress-induced apoptosis and ferroptosis, as well as the activation of autophagy. Our research also correlates the observed synergistic effects between curcumin and conventional chemotherapeutic agents. Finally, the results provide a theoretical basis for understanding the correlation between GRDs and the biological mechanism of action of curcumin at the quantum level, corroborating its potential as a complementary therapeutic agent in the treatment of lung cancer.

Keywords

apoptosis; A549 cell; curcumin; density functional theory; global reactivity descriptors; lung cancer; reactive oxygen species

Introduction

Lung cancer remains a leading cause of death worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of these cases and is responsible for about 1.7 million deaths annually [1]. This reality underscores the need to innovate and develop more effective and selective therapeutic agents, such as curcumin. Curcumin, a derivative of *Curcuma longa*, has been proposed in recent research as a candidate for cancer chemoprevention and treatment. Numerous *in vitro* and *in vivo* studies document and demonstrate its ability to inhibit cell proliferation and induce apoptosis in the A549 NSCLC cell line [1-5]. Curcumin utilizes diverse mechanisms for its biological action, including its ability to induce oxidative stress, inhibit histone deacetylase (HDAC) [1, 6-8], and

negatively regulate large non-coding RNAs (lncRNAs) [2], and induced non-apoptotic cell death pathways, such as ferroptosis [6, 8]. Recent reports on novel formulations such as dendrosomal curcumin (DNC) show greater potential, acting synergistically with conventional chemotherapeutic agents such as daunorubicin by modulating key apoptotic markers and gene expression [9]. This multimodal mechanism of action directly influences current antitumor drug discovery, focusing on the rational design of synthetic hybrid compounds. Inspired by the polypharmacology of curcumin, these novel agents are designed to act simultaneously on multiple therapeutic targets, such as key enzymes (COX-2, HDAC, topoisomerase II), tyrosine kinase receptors (EGFR, VEGFR-2), and cellular structures like tubulin. This multi-target strategy demonstrates how optimizing the electronic and structural properties of a ligand can enhance apoptotic efficacy, following the pharmacological principle exemplified by natural products like curcumin [10-15].

There is a lack of understanding of the quantum mechanical properties related to the biological action of curcumin, despite experimental evidence; in other words, its biochemical reactivity at the quantum level. Therefore, density functional theory (DFT) offers a powerful computational tool to understand how its molecular and electronic structure relates to its biological function, allowing for the quantum characterization of molecules using global reactivity descriptors (GRDs). GRDs such as ionization potential (*IP*), electron affinity (*EA*), chemical potential (μ), hardness (η), electronegativity (χ), electrophilicity index (ω), and softness (S) provide valuable information about the quantum behavior. Furthermore, the energies of the *HOMO-LUMO* frontier molecular orbitals and the energy gap are related to a molecule´s reactivity in its electron donation or acceptance, which is fundamental for predicting interactions with biological targets and various signaling pathways in the biological context [16-20].

The objective of our research is to corroborate and correlate what other has reported by other research on the effects of curcumin in relation to cancer, using DFT calculation to quantitatively characterize the electronic profile of curcumin from the perspective of quantum physics, in order to understand in the biological context the proapoptotic activity established in A549 cell.

Our hypothesis is that the electronic fingerprint of curcumin, through its GRDs, describes its biological action, specifically a high electrophilicity index, which constitutes the quantum mechanical basis of its ability to act as an electrophilic stress factor, interacting with nucleophilic biomolecules and thus triggering the signaling cascades that lead to programmed cell death.

Materials and methods

Computational details

To obtain the structural and physical properties of curcumin through computational simulations, we performed the following research protocol. First, we constructed the molecular structure of curcumin ((1E, 6E)-1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione) using information from the PubChem database and the DMol3 tool in Material Studio. Subsequently, we optimized the molecular structure using Density Functional Theory (DFT) to determine its lowest binding energy and physical properties. To describe the exchange-correlation effects, we employed the generalized gradient approximation (GGA) with the Perdew-Wang functional 91. We included a DFT-D3 dispersion correction with the TS (Tkatchenko-Scheffler) scheme to account for nonbonding interactions, particularly van der Waals forces. Finally, we simulate the solvation effects of the aqueous biological environment using a conductor-type screening model (COSMO) with the dielectric constant of water ($\varepsilon = 78.36$) [16-20].

Calculation of global reactivity descriptors

Following geometric optimization, we directly obtained the energies of the frontier molecular orbitals: the highest occupied molecular orbital (*HOMO*) and the lowest unoccupied molecular orbital (*LUMO*), from the convergent calculation. We calculated the *LUMO-HOMO* energy gap (ΔE) as the difference between these two energies. We derived the global descriptors from the total energies of the system in its neutral (N), anionic (N+1), and cationic (N-1) states, denoted as E(N), E(N+1), and E(N-1), respectively. We used these energies to calculate key parameters within the DFT conceptual framework, applying the following equations with absolute energy values [16–20]:

Ionization potential (*IP*): $IP = E(N-1) - E(N)$ (1)

Electron affinity (*EA*): $EA = E(N) - E(N+1)$ (2)

Chemical potential (μ): $\mu = -(IP + EA)/2$ (3)

Chemical hardness (η): $\eta = (IP - EA)/2$ (4)

Electronegativity (χ): $\chi = (IP + EA)/2$ (5)

Electrophilicity index (ω): $\omega = \mu^2/(2\eta)$ (6)

Softness (S): $S = 1/(2\eta)$ (7)

Results

Optimised Molecular Structure and Electronic

Distribution

The ground-state geometry of curcumin ($C_{21}H_{20}O_6$, molecular weight 368.4 g/mol), composed of 47 atoms and an electron density of 194 electrons, was optimized using Density Functional Theory (DFT) in an aqueous solvation model, yielding the most stable conformation shown in Figure 1. Subsequent in silico analysis of the optimized electronic structure of curcumin revealed the spatial distribution of the frontier molecular orbitals, which are important for understanding chemical reactivity. The highest energy occupied frontier molecular orbital (*HOMO*) and the lowest energy unoccupied frontier molecular orbital (*LUMO*) are shown in Figure 2. The *HOMO-LUMO* orbitals define the regions of the curcumin molecule most susceptible to electronic interaction, particularly regulating its propensity to donate or accept electrons. Therefore, *HOMO-LUMO* analysis provides important information about electronic structure, polarizability, and chemical reactivity, which is fundamental for quantum-mechanical molecular characterization according to Fukui's theory [20].

Global reactivity descriptors (GRDs)

The GRDs calculated for curcumin, derived from the optimized structure and electronic energies, presented in Table 1. These include the chemical potential (μ), hardness (η), electronegativity (χ), softness (S), and electrophilicity index (ω), which together characterize the overall electronic fingerprint (electronic profile) of the curcumin molecule. Based on *in silico* analysis using DFT, these GRDs provide a robust and quantitative theoretical framework for predicting the chemical behavior and reactivity trends of curcumin in its biological context, relating them to experimental reports [16-20].

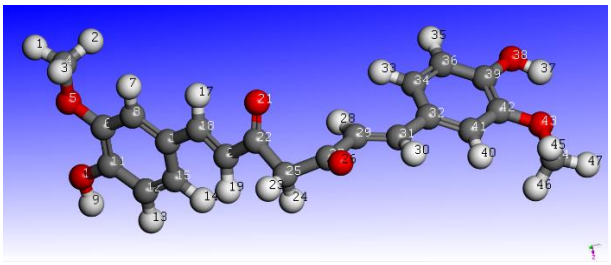

Figure 1: Optimized molecular structure of the ground state of curcumin ($C_{21}H_{20}O_6$) obtained using Density Functional Theory (DFT) calculations. Atomic color scheme: oxygen (red), carbon (gray), hydrogen (white).

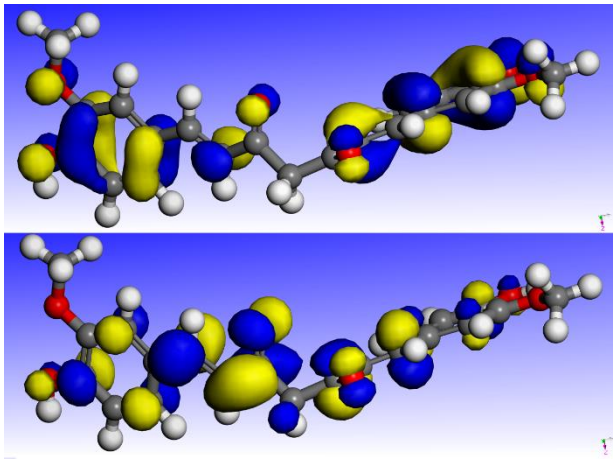

Figure 2: Electron density surfaces of the frontier molecular orbitals of curcumin, represented in globular structures in blue and yellow. The highest occupied molecular orbital (*HOMO*, top, -6.0489 eV) localizes the regions most susceptible to nucleophilic attack, while the lowest unoccupied molecular orbital (*LUMO*, bottom, -1.8385 eV) indicates the areas prone to electrophilic attack. The orbitals have an isosurface value of 0.02 a.u.

Table 1: Global Descriptors of Curcumin

Descriptor*	Energy eV
E (N-1)	-239.3770
E (N)	-244.3480
E (N+1)	-247.2990
EA	2.9510
IP	4.9710
μ	-3.9610
η	1.0100
X	3.9610
S	0.9901
ω	7.7671
HOMO	-6.0489
LUMO	-1.8385
$\Delta E \approx$	4.2104

*The abbreviations correspond to: Molecular charge -1, 0, 1 (*E(N-1), E(N), E(N+1)*); electron affinity (*EA*); ionization potential energy (*IP*); chemical potential (μ); chemical hardness (η); electronegativity (χ); softness (S eV^{-1}); electrophilicity (ω); frontier molecular orbitals (*HOMO, LUMO*); *LUMO-HOMO* gap ($\Delta E \approx$).

Discussion

This quantum-chemical characterization of curcumin establishes a solid electronic basis for its known pro-apoptotic efficacy in A549 lung cancer cells. The calculated reactivity descriptors collectively portray a molecule of

high inherent reactivity. This reactivity predisposes it to critical interactions within the cellular environment. Curcumin can easily transfer electrons due to its narrow *HOMO-LUMO* energy gap of 4.21 eV. Global reactivity descriptors (GRDs) correlate its pro-apoptotic effectiveness (see Table 1). Specifically, its low chemical hardness, high softness, and electrophilicity index. These values are consistent with Pearson´s hard and soft acid and base (HSAB) principles, classifying curcumin as a soft molecule [21], exhibiting high polarizability and a thermodynamic tendency to form covalent bond.s with complementary soft nucleophiles, common in biological system [22].

Induction of Oxidative Stress, Apoptosis, and Pyroptosis

The electron-donating capacity of curcumin is determined by its ionization potential (*IP*=4.97 eV), contributing to its pro-oxidant effects. Its highly electrophilic nature allows it to deplete the main cellular antioxidant, glutathione (GSH), possibly through Michael addition reactions [8]. This high depletion alters intracellular redox homeostasis, resulting in a high accumulation of reactive oxygen species (ROS) [1, 6]. This ROS accumulation generate oxidative stress, which acts as a potent trigger of apoptosis, mediated by mitochondrial membrane depolarization and consequent activation of stress response pathways, such as JNK and p38 MAPK [1]. The reported inhibition of histone deacetylases (HDACs) by curcumin correlates with softness (S=0.99 eV^{-1}) and electrophilicity (ω= 7.7 eV), through the covalent modification of nucleophilic residues in the enzyme´s active sites, a behavior also exhibited by its derivate CU17 [7]. Curcumin not only increases ROS, it also induced pyroptosis in A549 cell of NSCLC, inhibiting the E3 ligase Smurf2. By blocking it, stable NLRP3 accumulates, allowing the assembly of the inflammasome and gasdermin D to break the cell membrane forming pores, which leads to high inflammation, corroborating its electrophilic index (ω=7.7 eV) of curcumin in the regulation of the ubiquitin-proteasome system and inflammatory cell death [22].

Promoting Ferroptosis

We observed a significant correlation between the electrophilic nature of curcumin and its ability to induced ferroptosis. The functional stability of the GSH-GPX4 axis, which constitutes the main cellular defense pathway against this type of cell death, depends critically on the availability of glutathione (GSH). Our results indicate that the electrophilic property of curcumin mediates the direct decrease of intracellular GSH stores. This decrease leads to the subsequent inhibition of GPX4, a nucleophilic enzyme susceptible to this type of chemical modulation. The neutralization of cellular lipid peroxidation is compromised by the action described above, which accelerates the iron-dependent non-apoptotic cell death pathway, as has been experimentally reported [6, 8]. In cancer stem cell populations (A549 CD133+), this effect is evident, as curcumin acts on the two regulatory pathways of ferroptosis (GSH-GPX4 and CoQ10NDAPH), exhibiting an effective response [8].

Regulation of Genes Expression and its Relationship with the Cell Cycle and the Immune Response

The results of the quantum-mechanical characterization show that curcumin has a chemical potential (μ=-3.96 eV) that is related to its ability to influence intracellular signaling pathways and modulate gene transcription. This reactive capacity allows in repressing the expression of long non-coding RNAs with pro-oncogenic functions, such as UCA1, associated with a lower rate of cell division and stimulation of programmed cell death in neoplastic cells [2]. Various synthetic analogs derived from the basic structure of curcumin induce cell cycle arrest and promote the establishment of senescent state. This correlates with the behavior of curcumin, as a structurally related compound from the diarylpentanoid family has been shown to promote G0/G1 phase arrest, accompanied by senescence-like phenotypic characteristics in adenocarcinoma cell lines, thus generating prolonged restriction of tumor growth [22, 23].

Another relevant characteristic of curcumin is it pleiotropic action, where modulation of the immune system in the A549 cell line significantly attenuates interferon-gamma (IFN- γ)-induced PD-L1 overexpression, an action that depends on the reduction of STAT1 activation (phosphorylation) [24].

Our results indicate that the electrophilic functional groups present in the curcumin molecule, similar to those present in several pharmacological agent, could interact with critical nodes of tumor signaling networks, particularly the JAK/STAT cascade. This interference could neutralize the immune escape strategies employed by malignant cell, favoring elimination by cytotoxic T lymphocytes.

Modulation of Gene Expression and Broad-Spectrum Synergistic Efficacy

Our GRDs (see Table 1) correlate with results where curcumin can generate favorable interactions with various therapeutic compounds. This is confirmed by a research report in which curcumin-supplemented dendrosomal preparations significantly increase the cytotoxic activity of daunorubicin by modifying the balance between pro-apoptotic and anti-apoptotic proteins (increasing the Bax/Bcl-2 ration) and by reducing the expression of genes associated whit multidrug resistance, such as MDR-1 y hTER [9].

There are also scientific reports where curcumin increases the sensitivity of the A549 cell line to chemotherapeutic agents such as gemcitabine and paclitaxel [4, 5]. This increased sensitivity appears to depend on a prior modification of the intracellular environment mediated by ROS, as well as interference with signal transduction cascades that promote cell survival. Studies with structural analogues of curcumin, including the derivative known as CU17, have shown that their combination with gemcitabine produces a more intense antitumor response [25, 26].

To promote synergies, advanced drug delivery systems have been designed, such as the simultaneous coencapsulation of curcumin and gemcitabine on the same platform, resulting in a greater cytotoxic effect, as well as the simultaneous activation of different cell death pathways [27]. There are also reports indicating that curcumin and its derivatives exhibit antiviral and anti-inflammatory effect. In A549 cell infected with influenza-A virus, for example, these compounds attenuate the activation of RIG-I-dependent pathways [27], highlighting their ability to regulate the innate immune response against various pathogens.

According to our quantum mechanical analysis, curcumin behaves as a versatile electrophile that interferes with cellular redox balance, blocks key regulatory control enzymes, and modifies multiple programmed cell death pathways, including classical apoptosis, ferroptosis, and pyroptosis.

Our GRDs obtained in our *in silico* research establish a foundation for the rational development of structural derivatives of curcumin, including example such as the compound $ZYXO_2$-Na [3] and the analog CU17 [7, 25], as well as for the innovation of advanced drug delivery platforms [26]. Targeted structural modification of electronic properties (GRDs) in these derivatives emerges as an attractive pathway to increase their anticancer, antiviral, and immunomodulatory potency. The correspondence between their global quantum reactivity descriptors and multifaceted biological impacts highlights the value of curcumin as an adaptable molecular basis for multitarget therapeutic approaches, in which a single compound concurrently intervenes in several pathological processes or molecular targets [10-15].

Conclusions

Through quantum calculation, a theoretical model of curcumin was developed, which is valuable for guiding subsequent studies. The data obtained confirm curcumin´s ability to interact with critical intracellular targets associated with apoptosis activation in the A549 cell line. General reactivity descriptors support its biological profile, highlighting a high electrophilicity index and marked chemical reactivity. These properties position it as a highly reactive molecule with a remarkable capacity to adapt to the biological environment and the ability to trigger various programmed cell death mechanisms, such as apoptosis and ferroptosis. Curcumin´s ability to regulate multiple molecular pathways, combined with its roles as a synergistic enhancer in chemotherapeutic regimens, demonstrates its potential as a promising agent in the therapeutic approach to non-small cell lung cancer.

The integration of quantum mechanical computational analysis with experimental results validates the viability of curcumin and its structural analogs as effective therapeutic agents. Our results support the need for more experimental research and innovation aimed at applying these properties in optimized formulations, derivatives, or molecules that enable the development of more effective therapies against lung cancer.

List of abbreviations

COSMO: Conductor-like Screening Model
DNC: Dendrosomal curcumin
DFT: Density Functional Theory
EA: Electron affinity
eV: Electron volt
GGA: Generalized gradient approximation
GRDs: Global reactivity descriptors
GSH: Antioxidant glutathione
GPX4: Glutathione peroxidase 4 enzyme
G0/G1: Phases of the cell cycle
HOMO: Highest occupied frontier molecular orbital
HSAB: Pearson's Hard and Soft Acids and Bases
IP: Ionization potential
IFN-γ: Interferon-gamma
JNK: Signaling for apoptosis and autophagy
LncRNAs: Long non-coding RNAs
LUMO: Lowest unoccupied molecular orbital
MDR-1: Multidrug resistance 1
NLRP3: Innate immune system protein
NSCLC: Non-small cell lung cancer
p38/ MAPK: Signaling for apoptosis, inflammation, and genetic transcription.
ROS: Reactive oxygen species
RIG-I: Immune system receptor
STAT1: Transcription factor
TS: Tkatchenko-Scheffler

Author Contributions

All authors contributed equally to the preparation of the article: Conceptualization, methodology, and software: JC., AG., KI.; Validation, formal analysis, and fundraising: JC., FC., GR., FL.; Research, resources, data curation, writing (original draft preparation, revision, and ed-

iting), visualization, supervision, and project management: JC., AG., FC., GR., FL. All authors have read and approved the published version of the manuscript.

Availability of Data and Materials

The data supporting the results of this study are available upon request to the corresponding author.

Consent for Publication

No consent is required for publication, as the manuscript does not include personal data, images, videos, or any other material requiring consent.

Conflicts of Interest

The authors declare no conflicts of interest.

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Declared none.

AI-Declaration:

The authors confirm the use of DeepSeek (available at https://www.deepseek.com/) for grammar checking and enhancement of English fluency in the preliminary sections of the manuscript. The authors assume full responsibility for the content and results presented in this work.

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